

Consistency of Response with *Treximet*

This information is provided in response to your request for information about *Treximet*® (sumatriptan and naproxen sodium) Tablets. *Treximet* is a single-tablet formulation of sumatriptan 85 mg, formulated with RT Technology, and naproxen sodium 500 mg.

SUMMARY

- In two replicate double-blind, placebo-controlled, studies, *Treximet* consistently provided a statistically significant improvement over placebo for 2 hour pain free results and 2-24 hour sustained pain freedom across four migraine attacks. In addition, *Treximet* provided consistent freedom from pain in 2 out of 3 and in 3 out of 3 attacks within individual patients.
- Across two consistency of response studies, the overall incidence of adverse events was 9-13% of attacks within 72 hours of treatment with *Treximet* compared to 7-9% with placebo. The most common adverse events were dry mouth, nausea, dizziness, and somnolence.
- Important safety information is found in the attached Prescribing Information.
- The prescribing information for this product contains a boxed warning. Please consult the WARNING section of the attached prescribing information for further details and for important safety information.

CONSISTENCY OF RESPONSE OVER MULTIPLE MIGRAINE ATTACKS: STUDY DESCRIPTION

Two identical randomized, double-blind, multi-center, placebo-controlled, 4-period cross-over, multi-attack studies evaluated the consistency of response for *Treximet* when administered during the mild pain phase and within one hour of onset of headache pain for the acute treatment of migraine.^(1,2,3) Patients (n = 646 Study 1 and n = 620 Study 2) with International Headache Society criteria defined migraine with or without aura were randomly assigned to one of five treatment sequences (see Table 1).

A total of 570 and 565 patients, respectively, took at least 1 dose of study medication. The patient populations in both studies were predominately female and Caucasian, with a mean age of approximately 41 years (range 18-66). Patients were instructed to treat up to four eligible migraine attacks over a 4-month period. Rescue medication was allowed beginning two hours post-dose with the exception of ergot-containing compounds, barbiturates, opioids, or 5-HT agonists. The recommended rescue medication was two naproxen sodium 220 mg tablets, then one additional tablet (220 mg) six hours later if needed, not to exceed three tablets in a 24 hour period. Both studies evaluated *Treximet* versus placebo for the co-primary endpoints of consistency of two hour pain-free results and consistency of sustained pain-free results (2 - 24 hours) postdose across up to 4 migraine attacks. Secondary objectives included evaluation of within-subject consistency of response in attacks treated with *Treximet* and comparison of *Treximet* to placebo in incidence of associated symptoms of migraine (nausea, vomiting, photophobia, phonophobia), neck pain/discomfort and sinus pain/pressure, migraine-free (pain-free and no associated symptoms), satisfaction, recurrence of migraine pain, safety and tolerability.

Table 1. Consistency of Response Studies: Five Treatment Sequences (1,2,3)

	Attack 1	Attack 2	Attack 3	Attack 4
Group 1	P	T	T	T
Group 2	T	P	T	T
Group 3	T	T	P	T
Group 4	T	T	T	P
Group 5	T	T	T	T

T= *Treximet*; P = matching placebo

CONSISTENCY OF RESPONSE OVER MULTIPLE MIGRAINE ATTACKS: ACROSS ATTACK CONSISTENCY

Co-primary efficacy results are presented in Table 2.^(1,2,3)

Table 2. Consistency of Response Studies: Pain-Free at 2 Hours Post-Dose and Sustained Pain-Free Results 2-24 Hours Post-Dose (Using Repeated Measures Analysis)^(1,2,3)

	Study 1		Study 2	
	<i>Treximet</i> n = 1665	Placebo n = 422	<i>Treximet</i> n = 1655*	Placebo n = 416
2-Hour Pain-Free	52%†	25%	50%†	20%
Sustained Pain-Free‡	37%†	17%	34%†	12%

*n (attacks) = 1655 for 2 hour pain-free; n = 1656 for sustained pain-free

† $P < 0.001$ vs. placebo

‡Defined as pain free at 2 hours and maintenance of response through 24 hours post dose

In the repeated measures analysis, across all attacks taken together, *Treximet* produced a statistically significantly lower rate of associated symptoms (nausea, photophobia, phonophobia) at 2 and 4 hours ($P < 0.01$).^(1,2,3) At 2 and 4 hours post-dose, 43-44% and 66-69% of patients treated with *Treximet* were migraine-free (defined as free of migraine pain and associated symptoms of nausea, vomiting, photophobia and phonophobia), compared to 17-21% and 31-36%, respectively, for placebo ($P < 0.001$).

In both studies, in the supportive by-attack analysis, 2-hour pain-free results were significantly better in each attack treated with *Treximet* (47-53%) versus placebo (15-29%) ($P < 0.001$) as well as sustained pain-free rates (31-38% with *Treximet* versus 8-19% with placebo) ($P < 0.001$).

Data from the two studies were pooled and results were consistent with the individual studies.⁽⁴⁾

CONSISTENCY OF RESPONSE OVER MULTIPLE MIGRAINE ATTACKS: WITHIN-PATIENT CONSISTENCY

The percentages of subjects who reported pain-free results at 2 and 4 hours and sustained pain free results following initial treatment with *Treximet* are reported in Table 3. ^(1,2,3)

Table 3. Consistency of Response Studies: Within-Patient Consistency of Pain-Free and Sustained Pain-Free Results (1,2,3)

Attacks Treated with <i>Treximet</i> , n (% of patients)	≥1 of 2	≥2 of 3	3 of 3	≥3 of 4*	4 of 4*	All Attacks	≥1 attack
Study 1	n = 513	n = 487	n = 487	n = 95	n = 95	n = 558	n = 558
2-hour Pain-Free	349 (68)	268 (55)	140 (29)	50 (53)	27 (28)	159 (29)	397 (71)
4-hour Pain-Free	444 (87)	387 (80)	270 (55)	75 (79)	48 (51)	302 (54)	491 (88)
2-24 hour Sustained Pain-Free	262 (51)	174 (36)	71 (15)	29 (31)	9 (10)	83 (15)	322 (58)
Study 2	n = 517	n = 487	n = 487	n = 84	n = 84	n = 556	n = 556
2-hour Pain-Free	345 (67)	253 (52)	141 (29)	33 (39)	18 (21)	163 (29)	390 (70)
4-hour Pain-Free	439 (85)	368 (76)	259 (53)	60 (71)	37 (44)	300 (54)	490 (88)
2-24 hour Sustained Pain-Free	259 (50)	159 (33)	68 (14)	20 (24)	6 (7)	82 (15)	306 (55)
*Group 5 only – no placebo exposure							

For those patients who treated their first attack with *Treximet*, pain-free results for the second attack also treated with *Treximet* are reported in Table 4.(1,2,3)

Table 4. Consistency of Response Studies: Pain-Free Results in Responders and Nonresponders(1,2,3)

	Of responders, % of patients who responded on next attack n (%)	Of <u>non</u> responders, % of patients who responded on next attack n (%)
Study 1		
2-hour Pain-Free	190 (71)	82 (33)
4-hour Pain-Free	328 (84)	53 (43)
2-24 hour Sustained Pain-Free	118 (60)	66 (21)
Study 2		
2-hour Pain-Free	191 (71)	75 (31)
4-hour Pain-Free	308 (84)	74 (49)
2-24 hour Sustained Pain-Free	100 (55)	77 (23)

CONSISTENCY OF RESPONSE STUDIES: SAFETY

In study 1, the adverse event rates across the 4 treated attacks were 12%, 4%, 2% and 7% for placebo, respectively and 13%, 6%, 9% and 8%, for *Treximet*, respectively.(1,3) In study 2, the adverse event rates across the 4 treated attacks were 14%, 6%, 6% and 8% for placebo, respectively and 19%, 12%, 11% and 10% for *Treximet*, respectively.(2) (3)Adverse events on a treated attack basis are presented in Table 5.

Table 5. Consistency of Response Studies: Adverse Events Occurring Within 72 Hours After Treatment per Treated Attack – Safety Population(1,2,3)

	Study 1		Study 2	
	<i>Treximet</i> n = 1693	Placebo n = 424	<i>Treximet</i> n = 1678	Placebo n = 422
Attacks with any Adverse Event	153 (9%)	28 (7%)	219 (13%)	36 (9%)
Attacks with any Drug-Related Adverse Event	114 (7%)	19 (4%)	179 (11%)	24 (6%)

In study 1, the most common adverse events were nausea (1% with *Treximet*, <1% with placebo) and somnolence (1% with each treatment). (1,3) In study 2, the most common adverse events were dry mouth (3% with *Treximet*, 2% with placebo), nausea (3% with *Treximet*, 1% with placebo), dizziness (2% with *Treximet*, 1% with placebo) and somnolence (2% with *Treximet*, 1% with placebo).(2) (3)No serious adverse events considered to be drug related were reported in either study.

Enclosure: Prescribing Information for *Treximet* Tablets

Some information contained in this response may not be included in the approved Prescribing Information. This response is not intended to offer recommendations for administering this product in a manner inconsistent with its approved labeling.

In order for GlaxoSmithKline to monitor the safety of our products, we encourage healthcare professionals to report adverse events or suspected overdoses to the company at 888-825-5249. Please consult the attached Prescribing Information.

This response was developed according to the principles of evidence-based medicine and, therefore, references may not be all-inclusive.

REFERENCE(S)

1. Data on File. Study TRX103632 (RM2006/00565/00). 2007. *
2. Data on File. Study TRX103635 (HM2006/00568/00). 2007. *
3. Lipton RB, Dodick DW, Adelman JU, et al. Consistency of response to sumatriptan/naproxen sodium in a placebo-controlled, crossover study. Cephalgia 2009;online.*
4. Data on File. Study 103632/103635 (RM2007/00516/00). 2007. *